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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: PRODRUG COMPOUNDS AND PROCESS FOR PREPARATION THEREOF

(57) Abstract: The compound of the invention is a prodrug form of a therapeutic agent linked directly or indirectly to an oligopeptide, which in turn, is linked to a stabilizing group. More generally, the present invention may be described as a new prodrug compound of a therapeutic agent, especially prodrugs comprising an antitumor therapeutic agent, displaying improved therapeutic properties relative to the products of the prior art, especially improved therapeutic properties in the treatment of cancerous tumors and/or in the treatment of inflammatory reactions such as rheumatic diseases. Improved therapeutic properties include decreased toxicity and increased efficacy. Particularly desired are prodrugs which display a high specificity of action, a reduced toxicity, an improved stability in the serum and blood, and which do not move into target cells until activated by a target cell associated enzyme. Prodrug compounds of a marker enabling tumors to be characterized (diagnosis, progression of the tumor, assay of the factors secreted by tumor cells, etc.) are also contemplated. The present invention also relates to the pharmaceutical composition comprising the compound according to the invention and optionally a pharmaceutically acceptable adjuvant or vehicle. Further, a method of decreasing toxicity by modifying a therapeutic agent to create a prodrug is disclosed. Several processes for creating a prodrug of the invention are described. Compounds of the invention include the prodrugs, Suc-βAla-Leu-Ala-Leu-Dox, Suc-βAla-Leu-Ala-Leu-Dnr, and Glutaryl-βAla-Leu-Ala-Leu-Dox. Additionally intermediate compounds, important to the process of preparation of the prodrugs of the invention are claimed.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 05863 A (BAURAIN ROGER ; TROUET ANDRE (BE); UNIV LOUVAIN (BE); WALLONE REGIO) 29 February 1996 (1996-02-29) figures 3-5, 8, 11-13, 16-22, 25, 28-32 examples	66, 67
X	MASQUELIER, M. ET AL: "Incorporation and binding of anthracycline derivatives to low density lipoprotein: in vitro and in vivo studies on drug-LDL conjugates" RECENT ADV. CHEMOTHER., PROC. INT. CONGR. CHEMOTHER., 14TH, VOLUME ANTICANCER SECT. 1, PAGES 311-12. EDITOR(S): ISHIGAMI, JOJI. PUBLISHER: UNIV. TOKYO PRESS, TOKYO, JAPAN., XP000914544 page 311	66, 67



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30393

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KING, H. DALTON ET AL: "Synthesis and proteolytic cleavage of 3'-N- peptidyl -adriamycin prodrugs" PEPT.: CHEM., STRUCT. BIOL., PROC. AM. PEPT. SYMP., 11TH, MEETING DATE 1989, PAGES 137-9. EDITOR(S): RIVIER, JEAN E.; MARSHALL, GARLAND R. PUBLISHER: ESCOM SCI. PUB., LEIDEN, NETH., XP000914543 figure 1 table 1 ---	66,67
X	EP 0 037 388 A (INST INT PATHOLOGIE CELLULAIRE) 7 October 1981 (1981-10-07) examples 2A,4.2 ---	66,67
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Y	EP 0 640 622 A (DRUG DELIVERY SYSTEM INST LTD) 1 March 1995 (1995-03-01) page 13 ---	66,67
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X	UMEMOTO N ET AL: "PREPARATION AND IN-VITRO CYTOTOXICITY OF A METHOTREXATE-ANTI-MM46 MONOCLONAL ANTIBODY CONJUGATE VIA AN OLIGOPEPTIDE SPACER" INTERNATIONAL JOURNAL OF CANCER 1989, vol. 43, no. 4, 1989, pages 677-684, XP000120606 ISSN: 0020-7136 figure 1 page 681, right-hand column, last paragraph -page 682, left-hand column, line 4 page 682, right-hand column, line 13 - line 28 --- -/--	66,67

INTERNATIONAL SEARCH REPORT

Inter nal Application No

PCT/US 99/30393

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE MARRE ANNE ET AL: "Evaluation of the hydrolytic and enzymatic stability of macromolecular Mitomycin C derivatives." JOURNAL OF CONTROLLED RELEASE 1994, vol. 31, no. 1, 1994, pages 89-97, XP000456583 ISSN: 0168-3659 figures 3,4 page 95, right-hand column -page 96, left-hand column ---	66,67
Y	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US MASQUELIER, M. ET AL: "Antitumor activity of daunorubicin linked to proteins: biological and antitumor properties of peptidic derivatives of daunorubicin used as intermediates" retrieved from STN Database accession no. 97:150635 HCA XP002139800 abstract & CURR. CHEMOTHER. IMMUNOTHER., PROC. INT. CONGR. CHEMOTHER., 12TH, VOL. MEETING DATE 1981, VOLUME 2, 1428-30. EDITOR(S): PERITI, PIERO;GIALDRONI GRASSI, GIULIANA. PUBLISHER: AM. SOC. MICROBIOL., WASHINGTON, D. C., ---	66,67
Y	MASQUELIER, MICHELE ET AL: "Amino acid and dipeptide derivatives of daunorubicin. 1. Synthesis, physicochemical properties, and lysosomal digestion" J. MED. CHEM., 1980, VOL. 23, NO. 11, PAGE(S) 1166-70, XP000914522 abstract page 1167, paragraph RESULTS -page 1168 ---	66,67
Y	WALDMANN H ET AL: "ENZYMATIC PROTECTING GROUP TECHNIQUES" CHEMICAL REVIEWS,US,AMERICAN CHEMICAL SOCIETY. EASTON, vol. 94, no. 4, 1 June 1994 (1994-06-01), pages 911-937, XP000450393 ISSN: 0009-2665 page 911, paragraph INTRODUCTION page 912, paragraph 2.1 -page 914 ---	66,67
Y	WO 98 52966 A (CHRISTENSEN S BROGGER ;LILJA HANS (SE); DENMEADE SAMUEL R (US); IS) 26 November 1998 (1998-11-26) examples claims --- -/--	67

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/30393

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>ABOUD-PIRAK E ET AL: "CYTOTOXIC ACTIVITY OF DAUNORUBICIN OR VINDESINE CONJUGATED TO A MONOCLONAL ANTIBODY ON CULTURED MCF-7 BREAST CARCINOMA CELLS"</p> <p>BIOCHEMICAL PHARMACOLOGY 1989, vol. 38, no. 4, 1989, pages 641-648, XP000914578</p> <p>ISSN: 0006-2952</p> <p>page 642, right-hand column</p> <p>page 646, paragraph DISCUSSION -page 648</p> <p style="text-align: center;">-----</p>	66,67

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 67 in part, and 1-65

Present claims 1-65 relate to compounds, compositions and methods defined (inter alia) by reference to the following parameter(s):

P1: a therapeutic agent capable of entering a target cell

P2: a genetically-encoded or a non-genetically-encoded amino acid.

P3: a stabilizing group that hinders cleavage of said oligopeptide by enzymes present in whole blood.

P4: a linker group not cleavable by trouase.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible.

It is further pointed out, that the enzyme trouase is not sufficiently characterised in the description. This insufficiency also leads to a lack of clarity within the meaning of Article 6 PCT and to a lack of disclosure within the meaning of Article 5 PCT, especially since the enzyme trouase has not been mentioned with this name previously in the databases Medline, Cancerlit, Chemical Abstracts, Embase or Biosis, nor in the patent literature.

Moreover, present claims 1-65 relate to an extremely large number of possible compounds, compositions and methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds, compositions and methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Also, present claims 1-65 relate to compounds, compositions and methods defined by reference to a desirable characteristic or property, namely "the compound being selectively cleaved by an enzyme associated with the target cell". The claims cover all compounds, compositions and methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds, compositions and methods. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds, compositions and methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of claim 66, and to those intermediates of claim 67, which are indeed intermediates in the synthesis of the compounds according to claim 66.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 99/30393

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